PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	Docket No: Q93984
Atsushi NAGANAWA, et al.	
Appln. No.: 10/572,578	Group Art Unit: 1625
Confirmation No.: 2534	Examiner: Binta M. ROBINSON
Filed: March 17, 2006	

For: CARBOXYLIC ACID COMPOUNDS AND MEDICINAL COMPOSITIONS CONTAINING THE SAME AS THE ACTIVE INGREDIENT

DECLARATION UNDER 37 C.F.R. § 1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Yutaka OKADA, hereby declare and state:

1. THAT I am a citizen of Japan;

2. THAT I have received the Master Degree in Pharmacology from the University of Shizuoka in March of 1991;

3. THAT I have been employed by Ono Pharmaceutical Co., Ltd. since April 1991, where I hold a position with responsibility for research of arachidonic acid metabolite;

4. THAT I am one of the named inventors of the instant application;

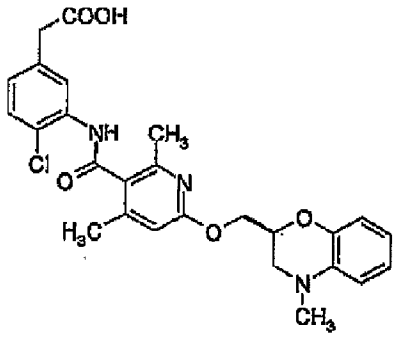
5. THAT I carefully reviewed the Office Action mailed on May 23, 2007 in this application and noted that the Office Action asserts, on pages 9-11, that the present application, while being enabled for the claimed compound (I) in which W is phenyl and J is benzoxazin-2-yl, benzofuran-3-yl, or benzodioxol-2-yl, is not enabled with respect to the compound (I) in which W is a cyclic group other than phenyl and J is an cyclic group other than above-mentioned three groups. In particular, it was noted that the Office Action asserts that the physiological activity such as DP receptor binding activity of a cyclic compound is unpredictable, and benzene ring (which is enabled by the specification of the present application) is non-basic, while other claimed compounds have a strongly basic ring structure, such as pyridine, and thus are not considered as being enabled.

6. In order to evaluate if physiological activity of a compound (I) is unexpectedly varied depending on the types of the substituents, in particular, the types of the ring W (e.g., if W is a basic ring or a non-basic ring), I performed the following experiment and confirmed that the results of the experiment show that compounds (I) exhibits a DP antagonistic activity regardless if the substitutent W is a basic ring or a non-basic ring.

7. Three compounds were tested in the following experiment: the compound of Example 13(2), the compound of Example 38, and a compound (I) ("test compound")(4-chloro-3-{[(2,4-dimethyl-6-{[(2S)-4-methyl-3,4-dihydro-2H-1,4-benzoxazin-2 methoxy]-3-pyridinyl}carbonyl)amino]phenyl}acetic acid). The test compound is identical to the

compound of Example 13(2) except the ring W is a pyridine ring, instead of a benzene ring. The test compound is selected because it has the W ring, which is a pyridine ring, and is structurally close to the compounds of Example 13(2) and Example 38.

8. The test compound is represented by the following general formula:



9. The following experimental method is identical to the procedure described in the specification of the instant application.

10. Measurement of Antagonistic Activity Against the DP Receptor Using Cells Expressing the Prostanoid DP Receptor:

CHO cells stably expressing the human DP receptor was constructed; seeded on a 24-well culture plate at a cell density of $1x10^5$ cells/well and incubated at 37°C for 2 days in 5% CO_2, Each well was washed with 500 μL of MEM (minimum essential medium) and the cells were incubated at 37°C for 10 minutes after adding 500 μL of MEM containing 2 μmol/L of

diclofenac. After removal of the supernatant by aspiration, 450 μL of an MEM containing 1 mmol/L 3-isobutyl-1-methylxanthine, 2 μmol/L diclofenac and 1% BSA (assay medium) was added, followed by incubation at 37°C for 10 minutes.

The reaction was initiated by addition of 50 μL of an assay medium containing PGD_2 and vehicle or an assay medium containing PGD_2 and the compound of the present invention (final concentration of PGD_2: 10 nmol/L), followed by incubation at 37°C. Ten minutes later, 500 μL of ice-cold trichloroacetic acid (TCA, 10% w/v) was added to terminate the reaction. After freezing (-80°C) and thawing the reaction mixture once, the cells were detached therefrom using a cell scraper followed by centrifugation at 13,000 rpm for 3 minutes.

The resultant supernatant was collected and cAMP concentration in the supernatant was determined by a enzyme immunoassay using a cAMP assay kit (manufactured by GE healthcare). A 500 μL aliquot of the above-prepared supernatant was mixed with 1 mL of 0.5 mol/L tri-n-octylamine in chloroform. After extraction of TCA into a chloroform layer, the amount of cAMP in an aqueous layer was quantified according to the procedure mentioned in the [^{125}I]cAMP assay kit.

Potency of the antagonistic activity of the compound of the present invention for the DP receptor was expressed was calculated as IC_{50} value (a concentration of the compound of the present invention which is necessary to suppress the cAMP production in the absence of the compound of the present invention by 50%) from inhibitory percentage to the cAMP production at 10 nmol/L, wherein PGD_2 elicited a submaximum cAMP production.

11. The test compound, 4-chloro-3-{[(2,4-dimethyl-6-{[(2S)-4-methyl-3,4-dihydro-2H-1,4-benzoxazin-2 methoxy]-3-pyridinyl}carbonyl)amino]phenyl}acetic acid, has a strong DP receptor antagonistic activity of IC_{50} value: 22 nmol/mL.

12. The compound of Example 13(2) of the instant application showed the IC_{50} value of 2.2 nmol/mL, and the compound of Example 38, (1-(4-chloro-3-((2,6-dimethyl-4-(((2S)-4-methyl-3,4-dihydro-2H-1,4-benzoxazin-2-yl)methoxy)benzoyl)amino)phenyl)cyclopropanecarboxylic acid) showed the IC_{50} value of 3.7 nmol/mL.

13. The compound of Example 13(2) is a compound in which R^{12} and R^{13} each are hydrogen and ring W is a benzene ring. The compound of Example 38 is a compound in which R^{12} and R^{13} are taken together to form a C2 alkylene and ring W is a benzene ring.

14. The present invention is directed to 1,3-substituted benzene derivatives represented by formula (1), and they are the compounds in which one of the substituents thereof is a carboxymethyl group and which have a bicyclic heterocycle as represented by dihydrobenzoxazin-2-yl, benzodioxan-2-yl, dihydrobenzofuran-2-yl, dihydrobenzofuran-3-yl and benzodioxol-2-yl at the end thereof.

15. The test compound employed in the experimentation is a compound in which R^{12} and R^{13} each are hydrogen and ring W is a pyridine ring. The DP antagonistic activity (IC_{50} value) of this compound was 22 nmol/mL.

16. In view of these results, one skilled in the art would reasonably expect that the compounds (I), in which R^{12} and R^{13} are taken together to form a C2 alkylene and ring W is a pyridine ring, have a DP antagonistic activity (IC_{50} value) of between a single digit to several dozen nmol/mL.

17. Also, the results of the experiment confirms that one skilled in the art would reasonably understand and expect that the compound of the present invention has a strong DP receptor antagonistic activity both in the case that ring W is a basic ring (e.g., pyridine ring) and in the case that ring W is a non-basic ring (e.g., benzene ring).

18. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: November 22, 2007

Yutaka Okada

Yutaka Okada